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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): 1385.45510X00

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Application Number	Filed
09/359,260	July 22, 1999

First Named Inventor: Robert L. CAMPBELL

Art Unit	Examiner
1631	DeJong, Eric S.

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- [ ] applicant/inventor.
- [ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- [X] attorney or agent of record. Registration number 39,397
- [ ] attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

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June 20, 2006
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

- [ ] *Total of _____ forms are submitted.

This collection of information is required by 35 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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ARGUMENTS FOR REQUEST FOR PRE-APPEAL CONFERENCE

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I. Independent Claims 135-138 and Dependent Claims 76, 82, 87-95, 131, 132, and 134 Are Not Anticipated

The Office Action does not make a *prima facie* case of anticipation predicated on the teachings of Ostrem. At the outset, Applicants would like to point out that the burden falls on the Examiner to establish a *prima facie* case of anticipation. See *In re Sun*, 31 USPQ2d 1451, 1453 (Fed. Cir. 1993). See also *In re Warner*, 154 USPQ 173, 177 (C.C.P.A. 1967), *cert. denied*, 389 U.S. 1057 (1968).

In order to qualify as an anticipatory reference, a prior art reference must also (1) disclose each and every element recited in the claimed invention, and (2) provide an enabling disclosure.

Regarding the first factor, Ostrem fails to disclose or suggest each and every step for a method of identifying peptides with a desired activity, as set forth in independent claim 135. Ostrem discloses a library for screening of biotinylated factor Xa-SAP mixture added to library beads. Beads that showed a blue color were destained, stripped, and further screened with the factor Xa-SAP-inhibitor mixture. Ostrem only identifies certain factor Xa inhibitors from an initial combinatorial library based on results obtained by assaying the beads.

Ostrem does not perform essential steps of independent claim 135, such as performing a space-filling design and constructing a first test peptide library. There is no evidence that Ostrem was actually attempting to construct a first test peptide library designed to provide any organized representation of, for example, the total octamer space. Ostrem does not even appear to mention of a space-filling design or provide some suggestion for a design that selects representatives from a plurality of compound isomers. Ostrem itself discloses that a complete representation of peptides in the library was not known, as only a select few peptides were confirmed as being available after activity assays were completed. Page 1054, col.1, lines 45-51). Another indication that the complete set of peptides in Ostrem's library screening

procedure was not known is the "split-synthesis methodology" used to generate the peptides. Typically, split synthesis methods are used when the goal is to synthesize and assay large libraries of peptides in a batch format, and not individually.

Ostrem also fails to disclose the claimed feature of parameterizing the predetermined peptides through determination of first and second parameters. The only measurements taken by Ostrem appear to relate to the potency of the peptides, a value which appears to be more consistent with measurement of an activity level, not the parameters.

Similarly, Ostrem provides no disclosure or suggestion for deriving a quantitative relationship between the measured indicia, the first parameter, and the second parameter, since these parameters are not measured. Ostrem merely tests peptides attached to the same beads. Ostrem does not provide any indication of how the inhibition of factor Xa activity relates to the first parameter or the second parameter. Furthermore, Ostrem never discusses a single formula that has been derived or any values that are calculated (not measured through assays) using this formula. Ostrem merely measures quantities such as the inhibition of Xa activity, and plots them in various graphs. Ostrem does not contain a single quantitative formula that is representative of these graphs.

Ostrem fails to disclose application of any derived quantitative relationship to calculate an estimated indicia for peptides remaining in the predetermined set of peptides. Ostrem measures the increased potency range of the initial leads identified in the combinatorial library. They are not calculated from a derived relationship as set forth in the claims. Furthermore, Ostrem appears to be completely silent on applying a quantitative formula to predict the potency of untested peptides.

Ostrem does not set a test requirement. Rather, Ostrem performs four separate assays of peptides identified from the initial set. It is unclear of how performing assays of peptides could possible read on, or even remotely suggest, calculating an estimated indicia using a derived quantitative relationship, as recited in the claims. Furthermore, the estimated indicia of the

claimed invention is calculated for peptides that remain from the predetermined set of peptides, i.e., peptides which are not included from the first test peptide library and have not yet been tested. In contrast, Ostrem never goes outside the original combinatorial library to identify peptides that have not been assayed and calculate an estimated value for the inhibition factor of Xa activity prior to performing an assay. In fact, Ostrem is completely silent about calculating and/or estimating any values. Ostrem appears to draw a "best fit" curve, or line, between the points that have been plotted on the graph. The curve plotted between measurements is not related to untested peptides. In fact, Ostrem provides no mention of the location where untested peptides would fall within any of the graphs. Ostrem does not even discuss untested peptides. Ostrem appears to be only concerned with peptides that have been tested.

There simply is no disclosure, or even suggestion, in Ostrem to indicate that a quantitative relationship is ever derived and subsequently applied to estimate parameters such as the inhibition of factor Xa activity prior to performing an assay of the peptide bound beads. Thus, there can be no realistic analogy to the claimed invention. Further, there are not citations to the exact location where Ostrem allegedly discloses the steps recited in the claimed invention. As previously indicated, an anticipatory reference must be enabling and must disclose all the claimed steps. The anticipation analysis presented in the Office Action appears tantamount to an application of the claims themselves as a blueprint to sustain the rejection.

Regarding the second factor, Ostrem fails to provide an enabling disclosure. In particular, Applicants note that it is the claimed invention (as defined by independent claim 135, for example) which must be enabled within the reference and not any other teachings disclosed by the reference. See *Elan Pharms. Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 68 USPQ2d 1373, 1375-76 (Fed. Cir. 2003) ("To serve as an anticipating reference, the reference must enable that which it is asserted to anticipate.")

Ostrem indicates that the initial peptides selected showed measurable performance characteristics when assayed in vitro. However, these same peptides failed to perform in their

intended in vivo application and the core motif required further modification to yield a functional peptide. As stated by Ostrem, "[A]lthough potent in chromogenic activity assays and *in vitro* coagulations assays, initial experimental work looking at half-life in rats following *i.v.* bolus injections showed that *N*-acyl, *N*-akyl peptides were inactivated or cleared from plasma within1-2 minutes." See page 1057, column 1, lines 5-9. In contrast peptides derived from the claimed process are capable of performing in their intended application without further modification. The disclosure of Ostrem cannot be considered enabling.

Ostrem simply fails to either disclose or suggest features that are explicitly recited in the claimed invention, such as:

> deriving a quantitative relationship between said indicia of said activity, said first parameter, and said second parameter;
>
> calculating an estimated indicia for each remaining peptide from said predetermined set of peptides using said quantitative relationship;
>
> setting a test requirement, based on a desired activity, having a test indicia range;
>
> selecting a second test peptide library comprising at least one second test peptide, wherein each second test peptide has an estimated indicia that satisfies said test requirement, and wherein said second test peptides are not in said first test peptide library;

Independent claims 136-138 each recite steps that are somewhat similar to those recited in independent claim 135. These steps are also not shown or suggested by Ostrem.

II. Independent Claims 135-138 and Dependent Claim 76, 82-95, 131, 132, and 134 Are Patentable

The Office Action does not make a *prima facie* case of obviousness predicated on the teachings of Ostrem and Cramer. First, there is no suggestion or motivation in Ostrem to modify, combine, or seek out the teachings of Cramer. Second, there is no realistic expectation of success from combining these references. Finally, the combination of references still fails to clearly teach or suggest all the limitations recited in independent claims 135-138.

Regarding the first factor, the Office Action also does not provide any credible indication as to where motivation exists, in Ostrem, to seek out the teachings of the teachings of Cramer for

purposes of arriving at the claimed invention. Cramer discloses a method of creating and searching a library (i.e., database) of potential molecules using validated molecular structural descriptors. Cramer appears to be concerned only with the database and data structure used to store the records pertaining to the molecules. For example, Cramer illustrates a table which stores a set of properties in an encoded form representative of a shape descriptor. At least one of these properties is indicated as being the hydrophobicity of the molecule. However, Cramer is not concerned with the screening of peptides and/or determination of desired activities. One skilled in the art would not seek out the teachings of Cramer to modify/improve the procedure described by Ostrem.

Regarding the second factor, the Office Action does not indicate why, or how, there could be a realistic expectation of success from combining these two references, which address different problems.

Regarding the third factor, even if the references were properly combinable, they would still fail to disclose or suggest all the features recited in claim 135. As previously discussed, Ostrem fails to disclose numerous features recited in independent claims 135-138. The inclusion of Cramer as a secondary reference does not to remedy this shortcoming. In addition, Cramer does not appear to disclose or suggest the features recited in claims 83-86, as alleged by the Office Action. Accordingly, the combination of Ostrem and Cramer would still be insufficient to render the claimed invention obvious. Cramer provides an overview of the use of compound libraries, while Ostrem provides a description for finding other low molecular weight peptide inhibitors of factor Xa. Neither the combination nor individual references teaches a method for finding compounds capable of enhancing cell culture media. Neither Ostrem nor Cramer provides details as to the percentage of undefined hydrolysate that can be present in media screening nor advantage gained with an adaptation culture.

For all the foregoing reasons, the pending rejections should be withdrawn.